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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,954	05/24/2002	Eric Samain	065691-0267	6242

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FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
PROUTY, REBECCA E	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 05/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,954	SAMAIN ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *15-17,21-24,29,31-38 and 40-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,18-20,25-28,30 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election without traverse of Group I, claims 1-39 in the reply filed on 1/13/05 is acknowledged. Applicants further elected the oligosaccharides lacto-N-fucopentaose and polylactosamine; the exogenous precursor lactose; and the recombinant genes β-1,3-N-acetyl-glucosaminyltransferase and β-1,4-galactosyltransferase. Applicants election of oligosaccharide lacto-N-fucopentaose was confusing as this oligosaccharide can not be made from the elected precursor with the elected enzymes. The examiner believed that applicants intent was in fact to elect lacto-N-neotetraose and polylactosamine as oligosaccharide. In a telephone interview on 4/1/05, Rob Norway confirmed that this was in fact applicants' intent. As such the office action is drawn Group I, lacto-N-neotetraose and polylactosamine as oligosaccharide, lactose as exogenous precursor and β-1,3-N-acetyl-glucosaminyltransferase and β-1,4-galactosyltransferase as the recombinant genes.

Claims 15-17, 21-24, 29, 31-38, and 40-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/13/05.

Claims 1, 7, 9 and 39 are objected to because of the following informalities: In claim 1, "and" should be inserted between steps (i) and (ii). In the interest of clarity, "chosen from" in claims 7 and 9 should be replaced with "selected from the group consisting of" and in claim 39 "a said" is grammatically incorrect. Appropriate correction is required.

Claim 25 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 25 recites a limitation already required in Claim 1 and thus is not further limiting.

Claims 1-14, 18-20, 25-28, 30, and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 (upon which Claims 3-14, 18-20, 25-28, 30, and 39 depend) is confusing in the recitation of "said precursor being involved in the biosynthetic pathway of said oligosaccharide" as it is unclear how this phrase modifies the scope of precursors recited as it is unclear how a precursor

could not be involved in the biosynthetic pathway of the oligosaccharide.

Claim 2 is confusing in the recitation "said enzyme being identical to or different that the enzyme used in the method described above" as it is unclear how the claim further limits claim 1 if the enzyme recited is identical to the enzyme in Claim 1. Furthermore, "used in the method described above is unclear" in which method is being referred to. It is assumed this means "in the method of claim 1".

Claim 2 is confusing in the recitation of "said cells lack any enzymatic activity liable to degrade said precursor" as it is unclear if "said precursor" refers to the endogenous precursor recited in line 4 of claim 2 or the exogenous precursor recited in claim 1.

Claim 4 is indefinite in the recitation of "a bacterium, preferably of *Escherichia coli* type" as it is unclear whether the feature following "preferably" is (a) merely exemplary and therefore not required, or (b) a required feature of the claim.

Claim 12 is indefinite in the recitation of "is at least 30%, preferentially 50% and, preferably 60%" as it is unclear whether the features following "preferentially" and "preferably" are (a) merely exemplary and therefore not required, or (b) a required feature of the claim.

Claim 14 is indefinite in the recitation of "carbohydrate nature, preferably of oligosaccharide nature" as it is unclear whether the feature following "preferably" is (a) merely exemplary and therefore not required, or (b) a required feature of the claim.

Claim 19 is indefinite in the recitation of "β-galactosides, preferably 4-O-β-D-galactopyranosyl-D-fructofuranose…" and "α-galactosides, preferably melibose…" as it is unclear whether the features following "preferably" are (a) merely exemplary and therefore not required, or (b) a required feature of the claim. Furthermore, the word "and" should be inserted prior to the final member of the group.

Claims 20 and 27 are confusing in the recitation of "said active transport" as the claims from which claim 20 and 27 depend do not require the transport of the exogenous precursor to be by active means.

Claim 30 is confusing as there is no antecedent basis for the terms "said substrate" and "said inducer" in claim 1 from which claim 30 depends.

Claims 1-14, 18-20, 25-28, 30, and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to methods of making any oligosaccharide intracellularly within any bacteria using a genus of enzymes and a genus of exogenous precursors. The specification teaches the production of only a few representative species of such methods which all use *E. coli* as the bacterium and only a very limited number of exogenous precursors and bacterial glycosyltransferase genes. The claims recite methods of producing any oligosaccharide from any exogenous precursor. While the art clearly teaches a few species of enzymes which can be used in the claimed methods, it is well known in the art that glycosyltransferases are highly specific to the type of saccharide linkage they produce. Furthermore, the vast majority of known glycosyltransferase genes are eukaryotic in origin and seldom can be expressed easily in bacteria. The art does not provide representative species of all genes which encode all possible enzymes within the scope of applicants claimed methods. Furthermore, there are an enormous number of potential precursor for oligosaccharides only some of which can be transported across the plasma membrane

of bacteria. While the specification teaches a few precursors which will clearly can enter into the cell or that the art provides a means of modifying a bacterium to allow transport of, the specification clearly does not teach sufficient representative species to allow a skilled artisan to utilize any precursor as most precursors would not be transported into the bacterium. Finally, the claimed methods recite the use of any bacterium, including the use of bacteria modified in a variety of ways to prevent the degradation of the oligosaccharide of interest. The specification clearly does not teach sufficient representative species of such bacteria as bacteria are highly diverse in their abilities to degrade carbohydrates as well as the pathways used to do so. As such, the modification of one bacteria such that it does not degrade a oligosaccharide of interest cannot be considered to be representative of the types of modifications which would be necessary for even that same oligosaccharide to be produced by any bacteria, and clearly would not be representative of the types of modification necessary for the production of other oligosaccharides. Given this lack of description of representative species of enzymes, bacteria, oligosaccharides, and exogenous precursors utilized in the claimed methods, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and

exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1-14, 18-20, 25-28, 30, and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of making lacto-N-neotetraose or polylactosamine from lactose using Lac Z^- *E. coli* transformed with the *Neisseria gonorrhoeae* LgtA and LgtB genes, does not reasonably provide enablement for methods of making any oligosaccharide from any exogenous precursor in any bacterium. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-4, 8-13, 25, 27, and 39 are so broad as to encompass methods of making any oligosaccharide from any exogenous precursor in any bacterium. The remainder of the claims recite additional limitations to one or more of these factors but in no case clearly specifies all three of these factors. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claims. It is well known in the art that oligosaccharides are a highly diverse group of compounds that encompass an enormous

diversity of monosaccharide units which can be linked to one another in a vast array of distinct types of linkages. It is further known in the art that each distinct linkage is generally catalyzed by a distinct enzyme (i.e., glycosyltransferase) and that glycosyltransferases that catalyze different linkages generally have little of no structural homology to each other. The claims recite methods of making any oligosaccharide in any bacterium, requiring the use of an enormous number of different glycosyltransferase genes. The specification teaches only a few such genes which clearly do not provide a skilled artisan the ability to catalyze the synthesis of any possible oligosaccharide linkage desired. Furthermore, the vast majority of known glycosyltransferase genes are eukaryotic in origin and seldom can be expressed easily in bacteria, even further limiting the scope of available glycosyltransferase genes which could be used in the claimed methods. The claimed methods also include the use of any compound as an exogenous precursor for the intracellular production of the oligosaccharide of interest. However, there are an enormous number of potential precursors for any oligosaccharide of interest only some of which can be transported across the plasma membrane of bacteria. While the specification teaches a few precursors which clearly can enter into *E. coli* or that the art provides a means of modifying a

bacterium to allow transport of, the specification clearly does not teach how to utilize any precursor nor allow a skilled artisan to modify any bacteria such that it could utilize any precursor as most precursors would not be transported into the bacterium and in most cases the art clearly does not provide means for the modification of bacteria to actively transport the precursor. Finally, the claimed methods recite the use of any bacterium, including the use of bacteria modified in a variety of ways to prevent the degradation of the oligosaccharide of interest. The specification clearly does not teach sufficient guidance for the use of any such bacteria as bacteria are highly diverse in their abilities to degrade carbohydrates as well as the pathways used to do so. As such, the modification of one bacteria such that it does not degrade a oligosaccharide of interest cannot be considered to provide guidance for the use of other bacteria as the types of modifications which would be necessary for even that same oligosaccharide to be produced by any bacteria would clearly be different in other bacteria and clearly would not would not provide guidance for the types of modifications necessary for the production of other oligosaccharides.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the

claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods of making any oligosaccharide from any exogenous precursor in any bacterium. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of methods of making oligosaccharides as claimed is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8, 14, 18, 19, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Koizumi et al.

Kozumi et al. teach the production of the trisaccharide globotriose in a LacZ$^-$ *E. coli* transformed with the *Neisseria gonorrhoeae* LgtC gene encoding an α-1,4-galactosyltransferase from exogenously provided lactose (see page 848-849). As such Kozumi et al. meets all limitations of the instant claims.

Claim 20 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kozumi et al.

Kozumi et al. is described above. It is not clear if the *E. coli* strain utilized by Kozumi et al. is Lac Y^+ or Lac Y^-. As Kozumi et al. successfully utilize lactose as an exogenous precursor, clearly the lactose is being internalized within the cells, suggesting that the strain is in fact Lac Y^+. If the strain is Lac Y^+, claim 20 is anticipated by Kozumi et al. However, if the strain lacks the Lac Y gene which is well known in the art to encode the lactose permease necessary for active transport of lactose across the plasma membrane of *E. coli*, it would have been obvious to one of skill in the art to reintroduce this gene back into the bacteria of Kozumi et al. as lactose is the precursor used by Kozumi et al. and the presence of an active lactose permease would provide higher intracellular levels of the precursor. A skilled artisan would reasonably expect that increasing the intracellular levels of the precursor would increase the amount of globotriose produced.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at

> the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27, 28 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kozumi et al.

Kozumi et al. is described above but do not specifically teach the use of an inducer such as IPTG for increasing the expression of the glycosyltransferase and/or the expression of the lactose permease gene. However, the lactose promoter of *E. coli* is well known in the art to be induced by IPTG. Furthermore, as high levels of intracellular lactose are clearly necessary to produce high levels of globotriose, it would have been obvious to induce the expression of the lactose permease gene (whether endogenous to the cells of Kozumi et al. or reintroduced as discussed above) with IPTG in order to ensure high levels of the precursor intracellularly.

Kozumi et al. further do not specifically teach the production of a radioactively labeled oligosaccharide. However,

as the use of radioactively labeled oligosaccharides is well known in the art it would have been obvious to use the methods of Kozumi et al. to produce radioactively labeled globotriose by including radioactively labeled lactose or galactose (i.e., the precursors of the globotriose) in the reaction.

Claims 9-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kozumi et al. in view of Bettler et al.

Kozumi et al. is described above but does not teach the production of globotriose using high cell density culture conditions or the use of glycerol as the carbon source.

Bettler et al. teach the intracellular production of the oligosaccharide βGal(1,4)[βGlcNAc(1,4)]$_4$GlcNAc using a LacZ$^-$ *E. coli* transformed with the *Azorhizobium* NodC gene encoding chitin pentaose synthase and the *Neisseria gonorrhoeae* LgtB gene encoding an β-1,4-galactosyltransferase using high cell density culture techniques as recited in claims 10-13 with glycerol as the carbon source and that these culture techniques lead to high production levels of the desired oligosaccharide.

As each of Kozumi et al. and Bettler et al teach the production of a desired oligosaccharide in a LacZ$^-$ *E. coli* transformed with the necessary glycosyltransferase genes for the production of the oligosaccharide from an available precursor,

it would have been obvious to a skilled artisan to apply the high cell density culture techniques taught by Bettler et al. to the oligosaccharide synthesis of Kozumi et al. with the expectation of increasing the amount of globotriose produced.

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kozumi et al. in view of Johnson and Gotschlich (WO 96/10086).

Kozumi et al. is described above but does not teach the production of lacto-N-neotetraose from lactose using a bacterium transformed with a β-1,3-N-acetyl-glucosaminyltransferase and a β-1,4-galactosyltransferase gene. However, Kozumi et al. clearly suggest the production of other oligosaccharides using as similar strategy to that used for globotriose production in *E. coli* transformed with other bacterial glycosyltransferase genes (see page 849).

Johnson et al. teach the production of lacto-N-neotetraose from lactose using bacterially expressed β-1,3-N-acetyl-glucosaminyltransferase and β-1,4-galactosyltransferase from *Neisseria gonorrhoeae* (see page 65).

Gotschlich teach the *Neisseria gonorrhoeae* LgtA and LgtB genes which encode the β-1,3-N-acetyl-glucosaminyltransferase and β-1,4-galactosyltransferase necessary for the synthesis of the

lacto-N-neotetraose structures found on the lipooligosaccharides of the bacteria and the use of these proteins for the synthesis of lacto-N-neotetraose.

Therefore, it would have been obvious to produce lacto-N-neotetraose intracellularly in a LacZ$^-$ *E. coli* transformed with the *Neisseria gonorrhoeae* LgtA and LgtB genes as Kozumi et al. clearly teach the usefulness of this system for the production of a variety of oligosaccharides, both Johnson and Gotschlich teach that lacto-N-neotetraose is a oligosaccharide of interest, Johnson show that this oligosaccharide can be produced using the β-1,3-N-acetyl-glucosaminyltransferase and β-1,4-galactosyltransferase from *Neisseria gonorrhoeae* and lactose as a precursor and Gotschlich teach the genes necessary for producing the transformed strain. Furthermore, while it is not clear if the *E. coli* strain utilized by Kozumi et al. is Lac Y$^+$ or Lac Y$^-$, as Kozumi et al. successfully utilize lactose as an exogenous precursor, clearly the lactose is being internalized within the cells, suggesting that the strain is in fact Lac Y$^+$. However, if the strain lacks the Lac Y gene which is well known in the art to encode the lactose permease necessary for active transport of lactose across the plasma membrane of *E. coli*, it would have been obvious to one of skill in the art to reintroduce this gene back into the bacteria of Kozumi et al. as

lactose is the suggested by Johnson and the presence of an active lactose permease would provide higher intracellular levels of the precursor. A skilled artisan would reasonably expect that increasing the intracellular levels of the precursor would increase the amount of lacto-N-neotetraose produced. Furthermore, as high levels of intracellular lactose are clearly necessary to produce high levels of lacto-N-neotetraose, it would have been obvious to induce the expression of the lactose permease gene (whether endogenous to the cells of or reintroduced as discussed above) with IPTG in order to ensure high levels of the precursor intracellularly.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1600